

## SUPPLEMENTAL MATERIAL

**Supplementary Table 1.** Spearman partial correlation coefficients\* between RBP4 markers and other biomarkers among controls, the Nurses' Health Study.

	Full-length RBP4 (µg/mL)	RBP4-L (µg/mL)	RBP4-LL ¶ (µg/mL)	RBP4-RNLL ¶ (µg/mL)	Total RBP4 (µg/mL)
Full-length RBP4 (µg/mL; n=472)	1.0	0.73†	0.10‡	0.10‡	0.95†
RBP4-L (µg/mL; n=472)	-	1.0	0.46†	0.18†	0.89†
RBP4-LL (µg/mL; n=472)	-	-	1.0	0.28†	0.31†
RBP4-RNLL (µg/mL; n=472)	-	-	-	1.0	0.16†
Total RBP4 (µg/mL; n=472)	-	-	-	-	1.0
HDL-C (mg/dL; n=465)	-0.01	-0.02	0.05	0.08	-0.01
LDL-C (mg/dL; n=461)	0.03	0.06	0.07	-0.01	0.05
Total cholesterol (mg/dL; n=465)	0.07	0.11‡	0.12†	0.05	0.10‡
Total to HDL-C ratio (n=465)	0.06	0.09	0.01	-0.06	0.07
Fasting TG (mg/dL; n=441)	0.09	0.14†	0.12†	0.04	0.12‡
CRP (mg/L; n=461)	0.01	0.06	0.07	0.07	0.03
Glomerular filtration rate § (n=472)	-0.06	-0.20†	-0.18†	-0.01	-0.13†
Adiponectin (µg/mL; n=463)	-0.02	-0.04	0.06	0.08	-0.01
Hemoglobin A1c (%; n=465)	0.02	0.04	0.06	0.01	0.03

Abbreviations: RBP4, retinol binding protein-4; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triacylglycerol; CRP, C-reactive protein.

\*Spearman correlation coefficients were adjusted for age at blood draw (yr), body mass index (kg/m<sup>2</sup>), fasting status (yes, no), smoking status (current smoker, past smoker, non-smoker), postmenopausal status (yes, no), hormone use (current user, past user, and non-user), physical activity (MET-hrs/week), alcohol use (g/day), family history of heart disease (yes, no), intakes of trans fat, polyunsaturated fat, and whole grains (all in tertiles), and use of aspirin. Glomerular filtration rate was further adjusted except when calculating the correlation coefficient for this variable.

†P<0.01

‡P<0.05

§Glomerular filtration rate =  $186 \times \text{Creatinine (mg/dL)}^{-1.154} \times \text{Age (yr)}^{-0.203} \times 0.742$

¶In the current investigation, we assigned the value of zero for levels of RBP4-LL and RBP4-RNLL that were below the detection limit.

**Supplementary Table 2.** Baseline (1989-1990) characteristics of CHD patients and controls by length of follow-up, the Nurses' Health Study.

Characteristics*	Follow-up time: 0-8 years			Follow-up time: 9-16 years		
	Cases (N=189)	Controls (N=188)	P value†	Cases (N=279)	Controls (N=284)	P value†
Age (year)‡	60.3 ±6.4	60.1 ±6.5	0.83	59.0 ±6.7	59.0 ±6.6	0.98
Body mass index (kg/m <sup>2</sup> )	26.8 ±6.0	25.5 ±4.5	0.01	26.2 ±4.6	25.1 ±4.1	0.003
Physical Activity (MET-hr/week)	14.1 ±13.5	17.1 ±16.2	0.05	18.6 ±20.0	18.6 ±17.6	0.99
Diet						
Whole grain (g/d)	15.7 ±13.0	16.4 ±10.9	0.60	17.4 ±12.0	16.2 ±11.1	0.22
Trans fat intake (g/d)	1.75 ±0.52	1.68 ±0.52	0.23	1.70 ±0.45	1.64 ±0.47	0.10
Polyunsaturated fat intake (g/d)	6.3 ±1.3	6.2 ±1.3	0.62	6.3 ±1.3	6.4 ±1.3	0.66
Alcohol (g/d)	5.1 ±9.2	6.3 ±9.0	0.22	5.9 ±8.5	7.2 ±10.1	0.09
Smoking status (%)‡			0.78			0.91
Current smoker	33.3	31.9		19.7	18.6	
Former smoker	32.8	34.0		41.2	41.6	
Never Smoked	33.9	34.0		39.1	39.8	
Medical history						
Diabetes (%)	21.2	5.3	<0.0001	8.6	4.9	0.08
Hypertension (%)	57.1	30.3	<0.0001	42.7	23.6	<0.0001
Hypercholesterolemia (%)	57.1	42.0	0.003	50.9	40.1	0.01
Parental MI before age 65 years (%)	33.9	20.7	0.004	30.8	18.7	0.0008
Fasting status (%)‡	68.3	65.4	0.56	72.4	73.9	0.68
Menopausal status (%)			0.24			0.92
Pre-menopause	9.5	13.8		12.5	12.7	
Menopausal, current hormone users	31.8	36.7		38.4	39.8	
Menopausal, past hormone users	21.2	15.4		16.1	17.3	
Menopausal, never used hormone	37.6	34.0		33.0	30.3	
Use of aspirin (%)	62.4	62.2	0.97	59.1	65.1	0.14
RBP4						
Full-length RBP4 (µg/mL)	72.9 (53.0,	63.0 (47.6,	0.008	61.6 (46.0,	61.9 (48.1,	0.93

	94.9)	83.0)		85.5)	88.0)	
RBP4-L (µg/mL)	28.9 (19.2, 38.1)	23.8 (18.0, 37.7)	0.11	25.3 (18.5, 34.7)	25.4 (18.3, 35.6)	0.87
Total RBP4 (µg/mL)	105.4 (71.7, 134.8)	88.1 (66.6, 125.4)	0.01	88.0 (67.7, 122.9)	91.1 (68.0, 126.2)	0.85
CVD risk markers §						
HDL-C (mg/dL)	49.7 (41.7, 61.0)	57.7 (48.2, 69.0)	<0.0001	52.0 (42.2, 63.7)	58.0 (48.1, 66.9)	0.0002
LDL-C (mg/dL)	146.1 (122.0, 169.0)	137.5 (111.1, 157.6)	0.006	136.7 (115.0, 163.0)	136.0 (110.4, 163.0)	0.32
Total cholesterol (mg/dL)	238.0 (211.0, 263.0)	223.0 (200.0, 255.5)	0.01	227.5 (205.0, 251.0)	224.0 (200.0, 254.0)	0.69
Total to HDL-C ratio	4.6 (3.8, 5.8)	3.8 (3.1, 5.0)	<0.0001	4.3 (3.4, 5.6)	3.9 (3.2, 4.7)	0.0002
Fasting TG (mg/dL)	128.0 (94.0, 200.0)	107.5 (77.0, 154.0)	0.0004	111.5 (81.0, 166.0)	101.0 (76.0, 143.0)	0.008
hsCRP (mg/L)	0.31 (0.12, 0.71)	0.20 (0.09, 0.44)	0.001	0.22 (0.10, 0.48)	0.16 (0.07, 0.33)	<0.0001
Adiponectin (µg/mL)	7.4 (4.7, 9.7)	8.6 (6.3, 11.2)	<0.0001	7.6 (5.4, 10.8)	8.7 (6.6, 11.5)	0.002
Hemoglobin A1c (%)	5.8 (5.5, 6.3)	5.6 (5.3, 5.8)	<0.0001	5.4 (5.2, 5.6)	5.3 (5.1, 5.5)	0.009
Glomerular filtration rate ¶	85.7 (71.6, 99.4)	76.2 (71.1, 86.4)	0.29	81.2 (69.6, 93.4)	76.2 (73.7, 83.8)	0.53

Abbreviations: MET-hr, metabolic equivalent-hour; MI, myocardial infarction; RBP4, retinol binding protein-4; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triacylglycerol; hsCRP, high-sensitivity C-reactive protein; CVD, cardiovascular disease.

\*Plus-minus values are mean ± standard deviation. Percentages are based on non-missing data. Levels of RBP-4 and other biomarkers are expressed as median (interquartile range) because of apparently skewed distributions.

†P value estimates are based on Student's *t* test for variables expressed as mean ± standard deviation, Wilcoxon rank-sum test for variables expressed as medians, or Pearson  $\chi^2$  test for variables expressed as percentages.

‡Matching factors.

§Data of total, HDL-cholesterol, and total/HDL-C ratio were missing for 12 participants, and the number of participants with missing values was 22 for LDL-C, 60 for TG, 20 for CRP, 13 for creatinine, 12 for hemoglobin A1c, and 14 for adiponectin.

¶Glomerular filtration rate =  $1.86 \times \text{Creatinine (mg/dL)}^{-1.154} \times \text{Age (yr)}^{-0.203}$

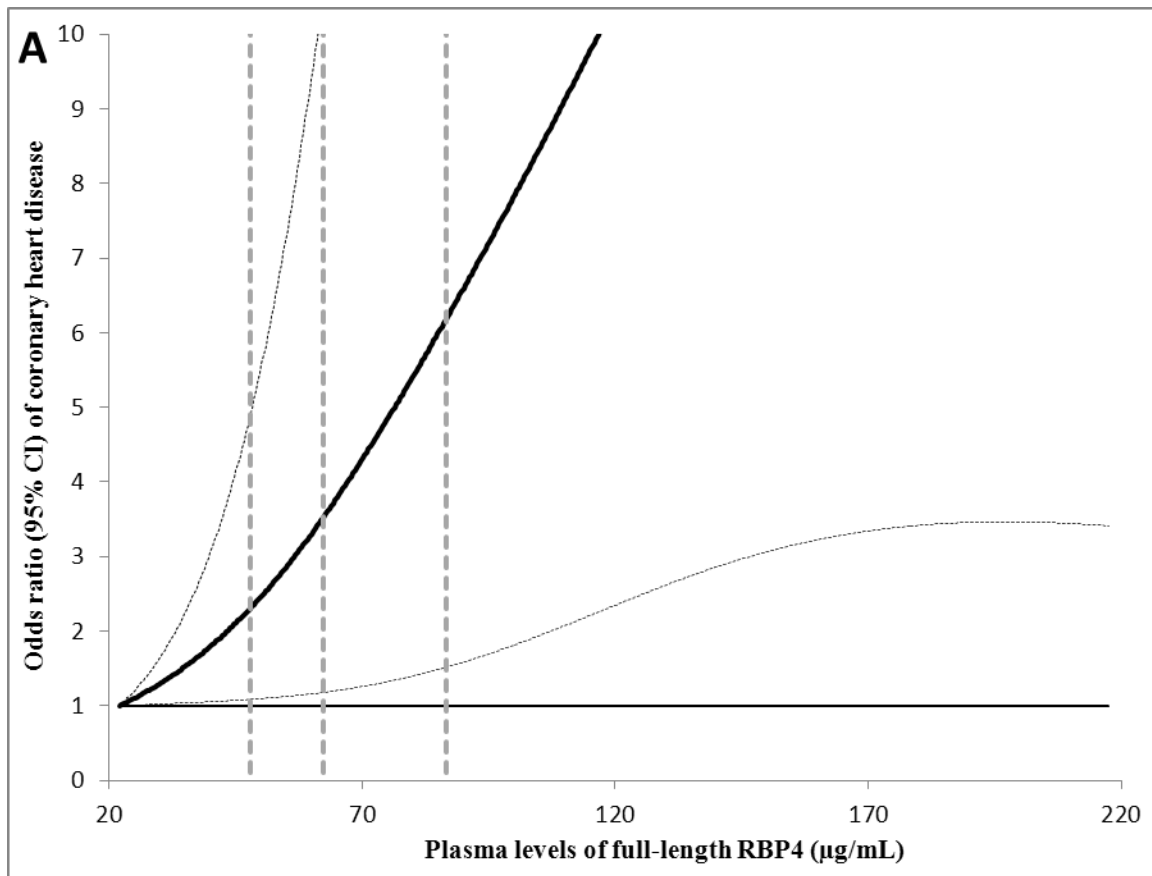
**Supplementary Table 3.** Odds ratio (95% CI) of CHD associated with RBP4 levels with stepwise adjustment of covariates\*, the Nurses' Health Study

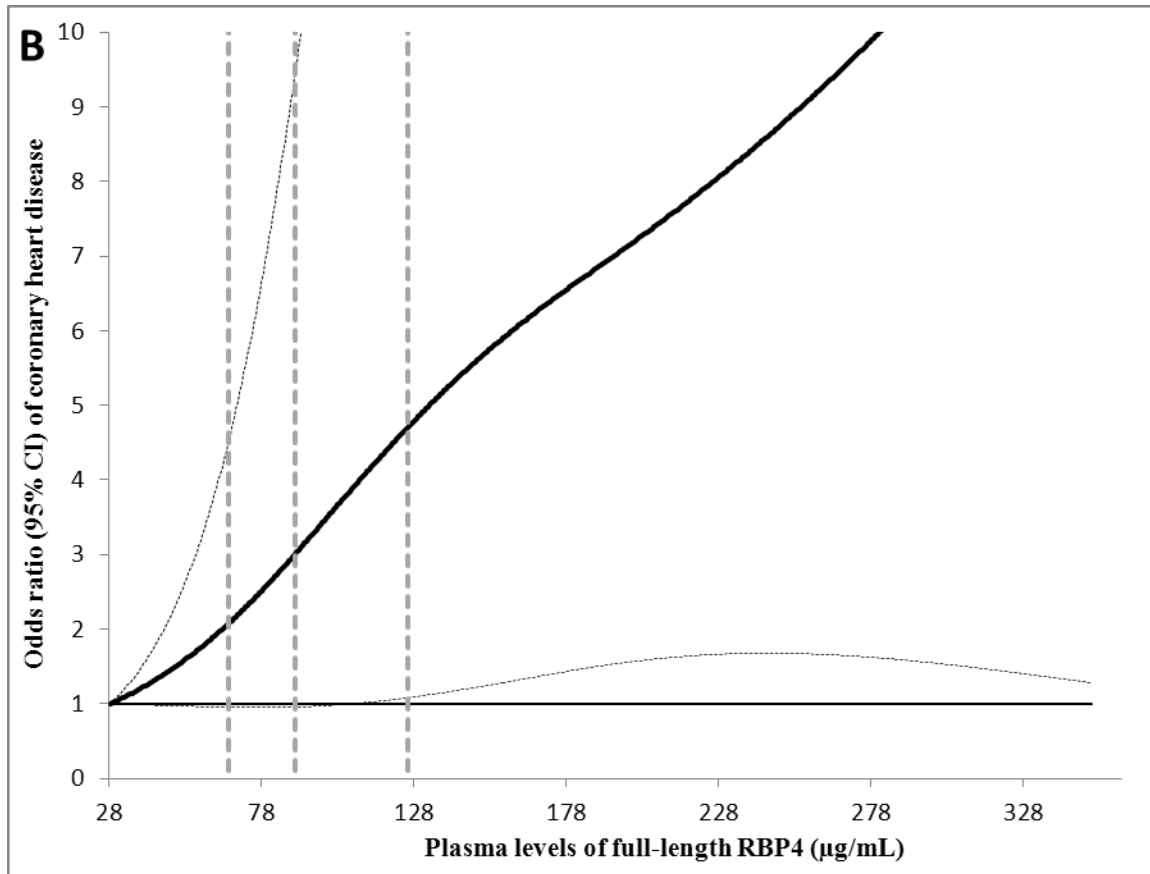
	First 8 years of follow-up				P <sub>trend</sub>
	Quartiles of RBP4 levels (µg/mL)				
	1 (lowest)	2	3	4 (highest)	
Full-length RBP4					
Median (range)	37.7 (22.1-47.9)	55.5 (48.0-62.4)	72.9 (62.5-85.9)	106.3 (86.9-217.5)	
Case/control	40/48	29/43	55/54	65/43	
Matching factors	1.0	0.96 (0.48, 1.93)	1.72 (0.83, 3.56)	2.92 (1.34, 6.38)	0.002
Dietary factors†	1.0	0.80 (0.38, 1.68)	1.41 (0.66, 3.03)	2.55 (1.13, 5.74)	0.003
Use of aspirin	1.0	0.80 (0.38, 1.68)	1.41 (0.66, 3.03)	2.54 (1.13, 5.74)	0.003
Glomerular filtration rate	1.0	0.80 (0.38, 1.69)	1.41 (0.66, 3.04)	2.51 (1.11, 5.67)	0.004
Physical activity	1.0	0.78 (0.36, 1.65)	1.37 (0.64, 2.96)	2.32 (1.02, 5.29)	0.008
Hypercholesterolemia	1.0	0.70 (0.32, 1.53)	1.28 (0.58, 2.82)	2.29 (0.98, 5.34)	0.008
Hypertension	1.0	0.62 (0.27, 1.41)	1.17 (0.50, 2.72)	2.20 (0.89, 5.48)	0.01
Menopausal status and hormone use	1.0	0.65 (0.28, 1.50)	1.34 (0.56, 3.21)	2.48 (0.97, 6.36)	0.007
Diabetes	1.0	0.69 (0.29, 1.67)	1.48 (0.59, 3.70)	2.89 (1.05, 7.90)	0.005
Alcohol	1.0	0.74 (0.31, 1.81)	1.63 (0.64, 4.17)	3.49 (1.21, 10.08)	0.003
Family history of MI	1.0	0.70 (0.29, 1.72)	1.57 (0.61, 4.05)	3.58 (1.22, 10.52)	0.003
Body mass index	1.0	0.70 (0.28, 1.72)	1.58 (0.61, 4.09)	3.56 (1.21, 10.51)	0.003
Blood lipids‡	1.0	0.71 (0.24, 2.09)	1.58 (0.54, 4.61)	3.30 (0.98, 11.13)	0.009
C-reactive protein	1.0	0.76 (0.26, 2.20)	1.40 (0.48, 4.10)	3.01 (0.87, 10.34)	0.02
Adiponectin	1.0	0.74 (0.24, 2.31)	1.61 (0.52, 5.00)	3.94 (1.05, 14.85)	0.01
HbA1c	1.0	0.61 (0.19, 2.01)	1.76 (0.52, 5.98)	4.45 (1.07, 18.51)	0.007

\*Each model was built based on the prior model by adding covariates one by one. The sequence was primarily based on the order through which each covariate was deleted from the backward selection.

†Intakes of whole grains, *trans* fat, and polyunsaturated fat (in tertiles).

‡Total cholesterol (mg/dL) and triacylglycerol levels (mg/dL).





**Supplementary Figure.** Odds ratio of coronary heart disease (95% CI) by levels of full-length and total RBP4 in the first 8 years of follow-up. In this analysis, we included all study participants. Multivariate conditional logistic regression models were adjusted for the same set of covariates for model 2 in Table 3a. Solid lines are ORs and dashed lines are 95% CIs. The dotted vertical lines represent the cut-off points for making quartiles listed in Table 3a. A, full-length RBP4; B, total RBP4.